REMARKS

Favorable reconsideration is respectfully solicited in view of the following remarks.

Initially, Applicant wishes to express its sincere thanks for the courtesy and cooperation provided to its undersigned representative by Examiner Thomas and Examiner Marschel during the personal interview held on March 13, 2008. The following is a summary of the items discussed during the interview.

Claim 19 has been amended as suggested by the Examiners to clarify that the claimed preparation has at least two components, the first component and the second component as described above.

Claims 39 and 40 have been amended consistent with the amendments to claim 19, to allow for rejoinder of these claims upon an allowance of claims 19-38.

New claims 41-63 have been added for additional patent protection. Claims 41-62 correspond to claims 19-40, respectively, except in reciting that the preparation "consists essentially of" the recited components. New claim 63 correponds to claim 19, except that the claim recites "consisting of" the recited components, together with optional components which are supported on page 12, lines 3-11 of the specification.

Turning to the Official Action, item 7 of the Official Action states that the Oath or Declaration is defective because it was not executed. An executed copy of the Declaration was filed on March 28, 2005. A check of the PTO image file history during the interview revealed that an executed copy of the Declaration has been received.

Accordingly, this defect is believed to be overcome.

Claims 19-24 and 31 are rejected under 35 U.S.C. 102 as anticipated by Gamache et al., WO 01/15677. This ground of rejection is respectfully traversed.

The subject matter of the present invention is directed to the specific combination of 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

On the other hand, Gamache et al. do not disclose this specific combination. Moreover the cited reference is directed to compositions comprising of 5-HT_{1D} and/or HT_{1B} agonists. The cited reference states that these agonists may be combined with an extensive list of other pharmaceutical agents, i.e. (1) anti-microbial agent, (2) anti-inflammatory agents or (3) anti-allergy agent (please see page 6, lines 1-3 of Gamache).

In addition, Gamache et al. only describes "bromfenac" as one of many examples of anti-inflammatory agents enumerated on page 12, lines 11-24. Gamache et al. does not concretely describe nor suggest the claimed preparation containing bromfenac.

Further, although tyloxapol (0.05% w/v) is added to an 1B/1D agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 (an Example of an otic/nasal suspension), there is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin is incorporated as a well-known antibacterial agent but is not an anti-inflammatory agent like bromfenac. Thus it is unclear from Gamache et al. why tyloxapol is added to the otic/nasal suspension containing 1B/1D agonist and moxifloxacin.

"Tyloxapol" described in Example 4 is just a single word description and does not give any clues and hints to the present invention. Therefore, the word "tyloxapol" described only in Example 4 does not destroy the novelty of the present invention.

Besides, Gamache et al. is silent about an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the preparation of the present invention.

Thus, Gamache et al. neither describe or suggest the specific claimed preparation of the present invention.

As discussed during the interview, it is respectfully submitted that the disclosure of Gamache et al. does not constitute an "anticipation" of the claimed invention under 35 U.S.C. 102. It is not possible to envision the specific claimed combination from the great number of possible combinations suggested by the cited reference.

As stated by the Board of Appeals in a similar case many years ago,

"While the invention here claimed in its broader aspect is doubtless embraced within the

speculative teachings of the references, we doubt if references which are not directed to the same purpose and do not have the same inventive concept, can be fairly applied in rejecting claims such as those on appeal where anticipation can be found only by making one of a very great number of possible permutations which are covered by the reference disclosures. The likelihood of producing a composition such as here claimed from a disclosure such as shown by the Dykstra patent would be about the same as the likelihood of discovering the combination of a safe from a mere inspection of the dials thereof."

Ex parte Garvey, 41 USPQ 583 (POBA 1939). See also Ex parte Starr, 44 USPQ 545 (POBA 1938); and Application of Luvisi, 52 CCPA 1063 (CCPA 1963).

See also M.P.E.P. 2131.02, discussing In re Meyer, 202 USPQ 175 (CCPA 1979) (A reference disclosing "alkaline chlorine or bromine solution" embraces a large number of species and cannot be said to anticipate claims to "alkali metal hypochlorite.").

For the foregoing reasons, it is respectfully submitted that the claimed invention is novel over Gamache et al.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection would be withdrawn.

Claim 19 is rejected under 35 U.S.C. 102 as anticipated by Dobrozsi, U.S. 6,319,513. This ground of rejection is respectfully traversed for the same reasons as stated above regarding the rejection over Gamache et al.

Dobrozsi discloses compositions comprising colloidal particles selected from the group consisting of silica, titanium dioxide, clay, and mixtures thereof. To the colloidal particle compositions may be added a great number of additional ingredients such as (1) analgesics, (2) decongestants, (3) expectorants, (4) antitussives, (5) antihistamines, (6) broncholilator, (7) topical anesthetics, (8) sensory agents, (9) oral care agents, (10) miscellaneous respiratory agents, (11) gastrointestinal agents, and mixtures thereof (please see column 2, lines 33-45 of Dobrozsi).

Dobrozsi describes on column 9, line 66 - column 10, line 11 that "[t]he analgesics useful for this invention include any narcotic and non-narcotic analgesics, such as --- bromfenac, ---". That is, Dobrozsi only describes "bromfenac" as one of so many examples of agents enumerated.

Further, Dobrozsi does not describe nor suggest an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the preparation of the

present invention.

Besides, Dobrozsi neither describes nor suggests the specific combination of 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester of the claimed invention.

Although tyloxapol is added to oxymethazoline hydrochloride in the preparation of mucoretentive intrasal spray decongestant (Example 10) on column 23, line 46 in Dobrozsi, no explanation about tyloxapol is given.

Besides, oxymethazoline hydrochloride is a well known adrenergic, and is not an anti-inflammatory agent like bromfenac.

For the same reasons as the 102 rejection over Gamache et al., it is respectfully submitted that the present invention is novel over Dobrozsi.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection would be withdrawn.

Claims 19-38 are further rejected under 35 U.S.C. 102(e) as being anticipated by Sawa, U.S. 2007/0082857. This ground of rejection is respectfully traversed.

The cited reference is a published U.S. patent application of a U.S. national stage application based upon PCT/JP04/16849 filed November 12, 2004. International Application No. PCT/JP2004/016849 was published in Japanese language under Publication No. WO2005/046700. Please see Appendix A. Accordingly, the published patent application has no 102(e) date, nor does the published international application WO2005/046700 have a 102(e) date. Please see Appendix B, which is a copy of Example 5 of the Examination Guidelines for 35 U.S.C. 102(e) published by the USPTO.

Accordingly, the earliest effective date of the cited reference as a prior art reference is its publication date of April 12, 2007. Moreover, the earliest effective date of the published international application WO2005/046700 is its publication date of May 26, 2005.

In conclusion, the cited reference is not available as prior art against the present invention, and this ground of rejection should be withdrawn.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection would be withdrawn.

Claims 19-29, 31-34 and 36-38 are rejected under 35 U.S.C. 103 as being unpatentable over Gamache et al. and ISTA Pharmaceuticals or Nolan et al. (abstract). This ground of rejection is respectfully traversed.

The essential features of the preparation of the present invention cannot be derived from the combination of Gamache et al. and ISTA Pharmaceuticals or Nolan (abstract).

Gamache et al. is discussed above. This reference does not suggest the claimed invention. Gamache et al. is directed to 5-HT agonist compositions with a great number of other possible ingredients. The reference does not suggest the claimed aqueous liquid preparation comprises at least the following two components according to claims 19-38, the first component comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Regarding claims 41-60, the claim recites the transitional phrase "consisting essentially of" means that the claim is limited to the specified ingredients and those that do not materially affect the basic and novel characteristics of the claimed invention. See M.P.E.P. 2111.03.

It is respectfully submitted that the principal 5-HT agonist of the Gamache composition would affect the basic novel properties of the claimed preparation.

The Examiners indicated during the interview that this amendment would be helpful to overcome this ground of rejection.

The cited ISTA publication was discussed during the interview. Although the cited reference has a publication date of May 25, 2004 after the effective U.S. filing date of the instant application, the reference is cited for its statement that "ISTA acquired U.S. marketing rights for Xibrom in May 2002 under a license from Senju." Thus the rejection is based upon the position that the claimed invention was known by others in the U.S. prior to the effective filing date of the instant application in the U.S. of January 16, 2004. And since the knowledgeable person(s) of ISTA is not an inventor of the invention, the reference is available as a reference under 35 U.S.C.

102(a), i.e. there is no one year grace period under 35 U.S.C. 102(b).

It should be noted that the cited reference does not disclose the claimed preparation. It does disclose a "bromfenac sodium ophthalmic solution", but it does not disclose the second claimed component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester. Nevertheless, it is understood that the PTO position is that the reference is being cited for the proposition that the claimed preparation was known in the U.S. by ISTA before the effective filing date of the instant application.

Upon inquiry, it has been determined that Xibrom has a different composition from the claimed preparation. Enclosed is a copy of the Product Insert and Material Safety Data Sheet as Appendix C. An examination of these documents show that Xibrom contains no alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester, which is the second component of the claimed preparation.

There is also enclosed a ISTA Press Release about Xibrom, which states that "Xibrom, under a different trade name but identical formulation, was launched in Japan in 2000 by Senju Pharmaceuticals Co. Ltd. ISTA acquired U.S. marketing rights for Xibrom in 2002 and launched the product in the U.S. in 2005." Please see the attached Appendix D.

In summary, the cited ISTA reference fails to suggest that the claimed preparation was known in the U.S. prior to the effective filing date of the instant application. Moreover the cited ISTA reference in combination with Gamache et al. does not suggest the claimed invention.

Regarding the alternative secondary reference Nolan, only the abstract of Nolan was cited in the rejection and included with the Office Action. The abstract only teaches that bromfenac is a potent anti-inflammatory agent. It does not disclose the claimed second component. Therefore the combination of Nolan (abstract) with Gamache et al. does not suggest the claimed preparation comprising the at least two components.

Applicant acknowledges that a complete copy of Nolan was provided to the Applicant's representative during the interview. The complete copy of the reference will be studied for its relevance and additional comments will be provided if possible.

Nevertheless, it is respectfully submitted that neither Gamache et al., ISTA

Pharmaceuticals and/or Nolan disclose or suggest the claimed preparation as amended, because they do not disclose the claimed preparation comprises the at least first and second claimed components.

Regarding new claims 41-60, even if one skilled in the art would have been motivated to modify the Gamache et al. composition in view of ISTA and Nolan, the artisan would have still obtained a 5-HT agonist composition, which is excluded from the amended claims by the "consisting essentially of" transitional phrase.

For the foregoing reasons, Applicant submits that the present invention is unobvious from Gamache et al. and ISTA Pharmaceuticals or Nolan to those skilled in the art.

Claims 19-30 are rejected under 35 U.S.C. 103 as unpatentable over Yakuji Nippo Ltd. and Xia, U.S. 6,369,112. This ground of rejection is respectfully traversed.

As stated in the rejection, the Yakuji reference teaches a bromfenac solution. It does not teach tyloxapol. Xia teaches adding tyloxapol to a contact lens solution to improve stability of the solution.

However Xia teaches adding tyloxapol to the contact lens solution for the purpose of improving stability of the biguanide disinfection agent in the solution. See the abstract and column 1, lines 10-12.

On the other hand, the claimed invention does not contain a biguanide. Furthermore the preparation of Yakuji contains bromfenac and does not contain any biguanide, according to the partial translation of record. Bromfenac is structurally very different from a biguanide.

Therefore it is respectfully submitted that one skilled in the art would not have been motivated to add tyloxapol taught by Xia to the composition of Yakuji for the purpose of stabilizing bromfenac.

Therefore, it is respectfully submitted that the present invention is unobvious from Yakuji Nippo Ltd. and Xia.

There is concurrently filed herewith an Information Disclosure Statement. As suggested by the Examiners, a complete English Translation of Yakuji is cited in the IDS and enclosed herewith. Also enclosed and cited is a corrected partial English translation of Yakuji.

Claims 19-38 are further rejected under 35 U.S.C. 103 as unpatentable over Yakuji Nippo Ltd. and Xia and Nolan (abstract). This ground of rejection is respectfully traversed.

The teachings of Yakuji and Xia are discussed above. Nolan (abstract) fails to remedy the deficiencies of Yakuji and Xia. There is no teaching or suggestion in the cited references for combining tyloxapol, or any alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester, with bromfenac, or a 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain the claimed preparation.

Accordingly, this ground of rejection is respectfully submitted to be overcome.

Applicant gratefully acknowledges the Examiners' indication during the interview that this ground of rejection should be overcome.

Lastly, claims 19-38 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending application Serial No. 11/755,662.

The Examiner is respectfully requested to hold this provisional ground of rejection in abeyance until a later date. Upon overcoming all other grounds of rejection, it is respectfully submitted that this provisional ground of rejection should be withdrawn and the application passed on to allowance.

In summary, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly such allowance is solicited.

Respectfully submitted,

Shirou SAWA et al.

By: 

Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
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WORLD INTELLECTUAL PROPERTY ORGANIZATION
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MAR 26 2008
PATENT & TRADEMARK OFFICE
BE IAP97

(WO/2005/046700) AQUEOUS SOLUTION PREPARATION CONTAINING AMINOGLYCOSIDE ANTIBIOTIC AND BROMFENAC

Latest bibliographic data on file with the International Bureau

Publication Number: WO/2005/046700 **International Application No.:** PCT/JP2004/016849
Publication Date: 26.05.2005 **International Filing Date:** 12.11.2004

Int. Class.: ***A61K 31/196*** (2006.01), ***A61K 31/7036*** (2006.01), *A61K 9/00* (2006.01)

Applicants: **SENJU PHARMACEUTICAL CO., LTD.** [JP/JP]; 5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi, Osaka, 5410046 (JP) *(All Except US)*.
SAWA, Shirou [JP/JP]; 366-1-105, Minamibefu 4-chome, Nishi-ku, Kobe-shi, Hyogo, 6512116 (JP) *(US Only)*.

Inventor: **SAWA, Shirou** [JP/JP]; 366-1-105, Minamibefu 4-chome, Nishi-ku, Kobe-shi, Hyogo, 6512116 (JP).

Agent: **IWATANI, Ryo**; ORIX Dojima Bldg. 3F, 1-31, Dojima 2-chome, Kita-ku, Osaka-shi, Osaka 530-0003 (JP).

Priority Data: 2003-384646 14.11.2003 JP

Title: AQUEOUS SOLUTION PREPARATION CONTAINING AMINOGLYCOSIDE ANTIBIOTIC AND BROMFENAC

Abstract: Stable and clear aqueous solution preparations comprising aminoglycoside antibiotics or a pharmacologically acceptable salt thereof and bromfenac being a nonsteroid antiinflammatory agent or a pharmacologically acceptable salt thereof.

Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
African Regional Intellectual Property Org. (ARIPO) (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW)
Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication Language: Japanese (JA)

Filing Language: Japanese (JA)

APPENDIX A

Examination Guidelines for 35 U.S.C. § 102(e), as amended by the American Inventors Protection Act of 1999, and further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002, and 35 U.S.C. § 102(g)

This notice sets forth the interpretation by the United States Patent and Trademark Office (USPTO or Office) of 35 U.S.C. §§ 102(e) and 374, as amended by the American Inventors Protection Act of 1999 (AIPA) (Pub. L. 106-113, 113 Stat. 1501 (1999)), and as further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002 (H.R. 2215) (Pub. L. 107-273, 116 Stat. 1758 (2002)). This notice also clarifies the Office's policy on prior art rejections based on 35 U.S.C. § 102(g).

Generally, 35 U.S.C. § 102(e), after enactment of the AIPA and H.R. 2215, is similar to the pre-AIPA § 102(e), with two significant differences, which may be summarized as: (1) in addition to U.S. patents, now certain **publications** of U.S. and international applications may be applied as of their filing dates in a prior art rejection; and (2) **certain international filing dates** are now U.S. filing dates for prior art purposes under § 102(e), and U.S. patents and certain application publications may now be applied as of these international filing dates in a prior art rejection.

Specifically, this notice provides guidance that prior art, as defined by § 102(e) of the patent code in effect on November 29, 2000, includes U.S. patents, publications of U.S. patent applications and World Intellectual Property Organization's (WIPO) publications of international applications, provided such references do not directly or indirectly result from an international application filed before November 29, 2000. If a U.S. patent resulted from an international application filed before November 29, 2000, the U.S. patent will have a prior art date per § 102(e) in effect prior to November 29, 2000, which is the earlier of the date of compliance with § 371(c)(1), (2) and (4) of the patent code (e.g. National Stage entry) or the filing date of the later-filed U.S. application that claimed the benefit of the international application. A U.S. or WIPO publication of an international application filed prior to November 29, 2000 will have no prior art effect under § 102(e). Such publications do, however, have prior art effect under § 102(a) or (b) as of their publication dates.

Furthermore, all pending U.S. patent applications being examined, and all U.S. patents being reexamined, or otherwise being contested, whenever filed, are subject to the amended version of § 102(e).

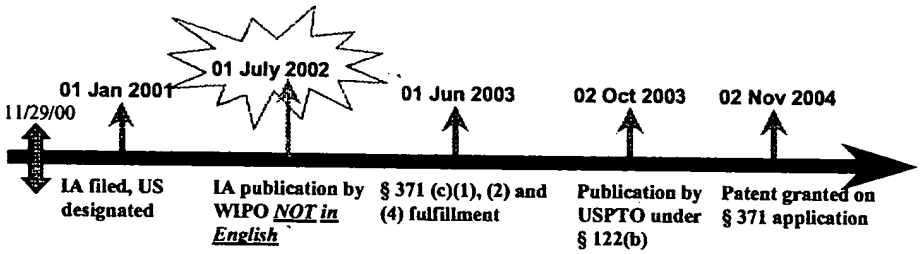
This notice also provides examples of the determination of § 102(e) dates for references based on the most common factual scenarios. The examples that best highlight the recent change to §§ 102(e) and 374 are the examples that involve a WIPO publication of an international application under PCT Article 21(2), a U.S. publication of an international application, or a U.S. patent derived from an international application.

The policy and practice set forth in the Official Gazette Notice entitled "Examination Guidelines for 35 U.S.C. § 102(e)(2), as amended by the American Inventors Protection

APPENDIX B

Example 5: References based on the **National Stage (§ 371)** of an **International Application filed on or after November 29, 2000** and which was **not** published in **English** under PCT Article 21(2).

All references, whether the WIPO publication, the U.S. application publication or the U.S. patent, of an international application (IA) that were filed on or after November 29, 2000 but were **not** published in **English** under PCT Article 21(2) have no § 102(e) prior art date at all. According to § 102(e), no benefit of the international filing date (nor any U.S. filing dates prior to the IA) is given for § 102(e) prior art purposes if the IA was published under PCT Article 21(2) in a language other than English. Such references may be applied under § 102(a) or (b) as of their publication dates, but never under § 102(e).



The § 102(e)(1) date for the IA publication by WIPO is: None
The § 102(e)(1) date for Publication by USPTO is: None
The § 102(e)(2) date for the Patent is: None

The IA publication by WIPO can be applied under § 102(a) or (b) as of its publication date (01 July 2002).

Additional Priority/Benefit Claims:

- ✓ If the IA properly claimed priority/benefit to any earlier-filed U.S. application (whether provisional or nonprovisional), there would still be no § 102(e) date for all the references.
- ✓ If a later-filed U.S. nonprovisional (§ 111(a)) application claimed the benefit of the IA in the example above, the § 102(e) date of the patent or publication of the later-filed U.S. application would be the actual filing date of the later-filed U.S. application.

Example 6: References based on the **National Stage (§ 371)** of an **International Application filed prior to November 29, 2000** (language of the publication under PCT Article 21(2) is not relevant)

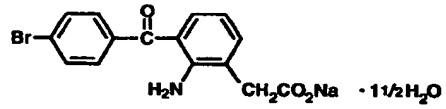
The reference U.S. patent issued from an international application (IA) that was filed prior to November 29, 2000 has a § 102(e) prior art date of the date of fulfillment of the requirements of 35 U.S.C. § 371(c)(1), (2) and (4). This is the pre-AIPA § 102(e). The

Xibrom™
(bromfenac ophthalmic solution) 0.09%

STERILE

DESCRIPTION

XIBROM (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of Xibrom contains 1.035 mg bromfenac sodium (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\ 1/2\ H_2O$. The structural formula of bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. XIBROM ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of XIBROM ophthalmic solution is approximately 300 mOsmol/kg. Each mL of XIBROM ophthalmic solution contains: **Active:** bromfenac sodium hydrate 0.1035%. **Inactives:** benzalkonium chloride (0.05 mg/mL), boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust the pH, and purified water, USP.

Clinical Pharmacology:

Mechanism of Action:

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Pharmacokinetics:

The plasma concentration of bromfenac following ocular administration of 0.09% XIBROM (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to each eye (0.09mg) and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans.

Clinical Trials:

Clinical efficacy was evaluated in two randomized, double-masked, vehicle-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥3 after cataract surgery were assigned to XIBROM or vehicle in a 2:1 ratio following surgery. One drop of XIBROM or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant effect of XIBROM on ocular inflammation after cataract surgery was demonstrated (62-66% vs. 40-48%). An additional efficacy end point was the time required for resolution of ocular pain in subjects who reported pain. Overall, only 20% of the patients undergoing cataract surgery in these trials had pain on the first day after surgery. In these patients, the XIBROM group demonstrated a statistically significant difference in median time to resolution of ocular pain of 2 days compared to 4 days for patients receiving vehicle.

Indications and Usage:

XIBROM ophthalmic solution is indicated for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction.

Contraindications:

XIBROM ophthalmic solution is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

Warnings:

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

There is the potential for cross sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

Precautions:

General:

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that XIBROM ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients:

XIBROM ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (360 times the recommended human ophthalmic dose [RHOD] of 1.67 µg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5.0 mg/kg/day (3000 times RHOD), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (540 and 180 times RHOD, respectively).

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (540 times RHOD) and in rabbits at oral doses up to 7.5 mg/kg/day (4500 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects:

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of XIBROM ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers:

Caution should be exercised when XIBROM ophthalmic solution is administered to a nursing woman.

Pediatric Use:

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use:

There is no evidence that the efficacy or safety profiles for XIBROM differ in patients 65 years of age and older compared to younger adult patients.

Adverse Reactions:

The most commonly reported adverse experiences reported following use of XIBROM after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2-7% of patients.

Clinical Practice: The following events have been identified during postmarketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown **(see PRECAUTIONS, General)**.

Dosage and Administration:

For the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction, one drop of XIBROM ophthalmic solution should be applied to the affected eye(s) two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

How Supplied:

XIBROM™ (bromfenac ophthalmic solution) 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap as follows:

NDC 67425-004-50 5 mL in 10 mL container
NDC 67425-004-12 2.5 mL in 7.5 mL container

Storage

Store at 15-25°C (59-77°F)

Rx Only

U.S. Patent No: 4,910,225

Manufactured for: ISTA Pharmaceuticals®, Inc., Irvine, CA 92618
By: Bausch & Lomb Incorporated, Tampa, FL 33637
Under license from: Senju Pharmaceuticals Co., Ltd., Osaka, Japan 541-0046
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XIB509-7/06

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APPENDIX C

ISTA Pharmaceuticals, Inc.
MATERIAL SAFETY DATA SHEET
Xibrom (bromfenac ophthalmic solution) 0.09%

PRODUCT AND COMPANY INFORMATION

Product Name:	Xibrom (bromfenac ophthalmic solution) 0.09%
Generic Name:	Bromfenac ophthalmic solution 0.09% (0.1% solution of Sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate)
NDC No.	67425-004-50 (5mL) and 67425-004-25 (2.5mL)
Legal Category:	Investigational drug, filled in bottle with controlled tip and overpacked inside a cardboard carton.
Drug Composition:	Contains a non steroidal anti-Inflammatory

Company Name: ISTA Pharmaceuticals, Inc.
Company Address: 15295 Alton Parkway, Irvine, CA 92618
Telephone Number: 949-788-6000 (Monday-Friday: 8:00am – 5:00pm PST)

Emergency Phone Number: 24 hours; Infotrack 1-800-535-5053

Preparation Date: May 03, 2005 (Version 05.03.05 – 01)

2. COMPOSITION/INFORMATION ON INGREDIENTS

Description	CAS#	TLV (mg/m^3)	PEL (mg/m^3)	% Content
Bromfenac Sodium Sesquihydrate	91714-93-1	NE	NE	0.1%
Sodium Borate	1303-96-4	NE	NE	>1%
Polyvinylpyrrolidone	252498-54-1	NE	NE	>1%
Purified Water	7732-18-5	NE	NE	>1%

Ingredients <1% - Boric Acid, Sodium Sulfite, Disodium Edetate, Polysorbate 80, Benzalkonium Chloride

3. HAZARDS identification

EMERGENCY OVERVIEW

Presents little or no hazards if spilled and no unusual hazard if involved in fire.

POTENTIAL HEALTH HAZARDS

Carcinogenicity: **(NTP)** No **(IARC)** No **(OSHA)** No

Eye: Irritant with some individuals

Skin: Irritant

Ingestion: Gastric exposure of large doses has been associated with ulceration and necrosis of gastrointestinal structures, as well as severe liver damage. Injestion of large doses may cause central nervous system effects, including drowsiness, dizziness, and vision disorders. Effects of injestion of lower doses, as present in the ophthalmic solution are unknown. Avoid unnecessary exposure.

Inhalation: Irritant.

Chronic Effects: Chronic ingestion of larger doses can cause severe liver damage. Chronic oral exposure of large doses may be associated with gastrointestinal disturbances, such as nausea, vomiting, heartburn and epigastric pain. Central nervous system effects may include drowsiness, dizziness, and vision disorders.

Target Organs: Liver, gastrointestinal system and central nervous system.

Medical Conditions Aggravated by Long Term Exposure: Avoid unnecessary exposure. Pre-existing liver or gastrointestinal conditions may be aggravated.

4. FIRST AID MEASURES

Eyes: Rinse immediately with copious amounts of water for at least 20 minutes. Contact a physician.

Skin: Remove all contaminated clothing and wash skin with copious amounts of water for at least 20 minutes. Contact physician if skin becomes irritated.

Ingestion: Wash out mouth and drink plenty of water and bland fluids. The use of an emetic drug and/or gastric lavage is advisable. Do not give anything to an unconscious person. Contact physician.

Inhalation: Remove person to fresh air, and if breathing stops, use artificial respiration. Contact physician.

Note to Physicians: The safety of this product in children has not been established.
Pregnancy: The safety of this product in pregnant women has not been established. This product should be used by pregnant women, or women who may be pregnant, only if expected therapeutic benefits outweigh the possible risks associated with treatment.

Nursing Mothers: The safety of this product in nursing mothers has not been established. This product should be used by nursing mothers, only if expected therapeutic benefits outweigh the possible risks associated with treatment.

Additional details are available on the package insert or in the Physicians Desk Reference.

5. FIRE FIGHTING MEASURES

Flammable Properties: Flash point: NE Method: NE

Hazardous Products: Products of combustion are toxic.

Extinguishing Media: Dry chemical, carbon dioxide, halon, water spray or fog, and foam on surrounding materials.

Fire Fighting Instructions: Wear self-contained breathing apparatus and protective clothing. Use water spray to keep fire-exposed containers cool. Do not spray water into the burning material.

6. ACCIDENTAL RELEASE

Large/Small Spills: Use personal protective equipment. Absorb spill with inert material (e.g. vermiculite, sand or earth), then place in suitable container. Contain the spill to prevent drainage into sewers, drains or streams. Dispose of material according to Federal, State and Local regulations.

7. HANDLING AND STORAGE

Handling: Avoid contact with product and use caution to prevent puncturing containers. No special protective equipment or procedures are required in the clinical or home environment.

Storage: Store product upright in original containers with the cap tightly closed at a controlled room temperature 15^0-30^0 C (59^0- 86^0 F). **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

8. EXPOSURE CONTROL/PERSONAL PROTECTION

Engineering Controls: When manufacturing this product in the manufacturing plant, provide adequate ventilation for the raw material handling and compounding process, which will maintain the dust and vapor levels below the TLV, STEL, and PEL values for the ingredients. Ventilation fans should be explosion proof. Use adequate personal protective equipment e.g. NIOSH-approved respirators, goggles or safety glasses, gloves and protective clothing. Ensure training in the handling of chemical material and use current Material Safety Data Sheets.

Eye Protection: (29 CFR 1910.133) Recommend goggles or chemical safety glasses when working with this product in the industrial setting.

Skin Protection: Thick impermeable gloves and protective clothing when manufacturing this product in the industrial setting.

Respiratory Protection: (29 CFR 1910.134) NIOSH approved respirator, with organic vapor, acid gas and HEPA filter recommended for handling raw materials. **Warning: Do not use air-purifying respirators in oxygen-depleted environments**. No respiratory protection is required in the clinical or home environment.

Other: None

Ventilation: Recommended in the industrial setting.

Contaminated Equipment: Wash contaminated clothing separately. Wash contaminated equipment with soap and water. Release rinse water into an approved wastewater system or according to Federal, State and Local regulations.

9. CHEMICAL & PHYSICAL PROPERTIES

Appearance & Odor: Clear Yellow Colored Solution

Boiling Point:	NE	Evaporation Rate:	NE
Specific Gravity:	1.0	Vapor Density:	NE
Vapor Pressure:	NE	Viscosity:	NE
Water Solubility:	Miscible	Percent Volatile by Volume:	<1

10. STABILITY AND REACTIVITY

Chemical Stability: Stable

Conditions to avoid: Extreme heat or cold.

Incompatibility: This product has the incompatibilities of water e.g. strong acids, bases, alkali metals, alkali hydrides and silver preparations.

Hazardous Decomposition Products: Products of combustion are toxic.

Hazardous Polymerization: Should not occur and has not been reported.

11. TOXICOLOGY

Summary of Risks: The toxicological information in this MSDS refers to the effects of the active ingredient (bromfenac sodium). Concentrations and toxicological effects are substantially reduced in the ophthalmic solution. For more detailed information see MSDS on bromfenac sodium (code 002990). Severe liver damage has been reported in patients who have taken multiple doses of an oral dosage form containing significantly higher concentrations of bromfenac sodium than are present in the ophthalmic solution.

CAS # 91714-93-1 **Bromfenac Sodium**
Bromfenac Sodium is known to cause liver damage in humans and or death when administered orally at therapeutic doses (at a concentration significantly higher than for the ophthalmic solution) for greater than ten days.

12. ECOLOGICAL INFORMATION

Chemical Fate Information: Product administered to patients presents a negligible impact on the environment.

13. DISPOSAL INFORMATION

Dispose of material according to Federal, State, and Local regulations. The method typically used is incineration.

EPA Designations: RCRA Hazardous Waste: Not Listed

SARA Title III: Not Listed

14. TRANSPORTATION INFORMATION

Transportation Data: Not classified as hazardous by DOT regulations.

15. REGULATORY INFORMATION

DOT Designations: Not classified as hazardous by DOT regulations.

EPA Designations: RCRA Hazardous Waste
(40 CFR 261.33) Not Listed

FDA Designations: Prescription only medication.
NDC No.: 67425-004-050 (5mL
and 67425-004-25 (2.5mL)

OSHA Designations: (29 CFR 1910.1000, Table Z)
Not Listed

SARA Title III: Not listed under Section 313 of Toxic Release Reporting.

CALIFORNIA PROPOSITION 65: Not Listed

16. OTHER INFORMATION

None

The information contained herein is furnished without warranty of any kind. The above information is believed to be correct but does not purport to be all-inclusive and should be used only as a guide. Users should make independent determinations of the suitability and completeness of information from all sources to assure proper use and disposal of these materials and the safety and health of employees and customers. In no way shall the company be liable for any claims, losses, or damages of any third party or for lost profits of any special, indirect, incidental consequential or exemplary damages, however arising, even if the company has been advised of the possibility of such damages.

NE- Not Established
< - Less Than
> - Greater Than

INVESTORS AND MEDIA

News Release

<< Back

ISTA Pharmaceuticals Submits New Drug Application for Xibrom(TM) QD (once-daily) 2007

IRVINE, Calif., Dec. 20 /PRNewswire-FirstCall/ -- ISTA Pharmaceuticals, Inc. (Nasdaq: ISTA), announced today the Company has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for Xibrom(TM) QD (once-daily). The Company is seeking approval for Xibrom QD as a treatment for inflammation, pain, and photophobia following cataract surgery.

Xibrom(TM) (bromfenac ophthalmic solution)

Xibrom is a topical non-steroidal anti-inflammatory compound for the treatment of ocular inflammation and pain. Xibrom, approved in 2005, is the first and only FDA-approved twice-daily NSAID for inflammation and reduction of pain following cataract surgery. Xibrom is the fastest growing ophthalmic product in 2007, according to IMS data. Xibrom, under a different trade name but identical formulation, was launched in Japan in 2000 by Senju Pharmaceuticals Co. Ltd. ISTA acquired U.S. marketing rights for Xibrom in 2002 and launched the product in the U.S. in 2005.

ABOUT ISTA PHARMACEUTICALS

ISTA Pharmaceuticals is an ophthalmic pharmaceutical company. ISTA's products and product candidates addressing the $3.2 billion U.S. prescription ophthalmic industry include therapies for inflammation, ocular pain, glaucoma, allergy, and dry eye. The Company currently markets three products and is developing a strong product pipeline to fuel future growth and market share. The Company's product development and commercialization strategy is to launch a new product every 12 to 18 months, thereby continuing its growth to become the leading niche ophthalmic pharmaceutical company in the U.S. For additional information regarding ISTA, please visit ISTA Pharmaceuticals' website at http://www.istavision.com.

SOURCE ISTA Pharmaceuticals, Inc.

CONTACT: Vince Anido, +1-949-788-5311, vanido@istavision.com, or Investors, Lauren Silvernail, +1-949-788-5302, lsilvernail@istavision.com, both of ISTA Pharmaceuticals; Media, Justin Jackson, jjackson@burnsmc.com, or Investors, Juliane Snowden, +1-212-213-0006, jsnowden@burnsmc.com, both of Burns McClellan, for ISTA Pharmaceuticals

APPENDIX D